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APPLICATION NO.	FILING DATE	FIRST NAME INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/701,121	01/03/2001	Shamir Karwar	146.1358	9941

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MUSERLIAN AND LUCAS AND MERCANTI, LLP  
600 THIRD AVENUE  
NEW YORK, NY 10016

EXAMINER
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HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
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1644

DATE MAILED: 02/10/2003

14

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/701,121

Applicant(s)

KAWAI ET AL.

Examiner

" Neon" Phuong Huynh

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-- The MAILING DATE of this communication appears on the cover sheet with the corresponding address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 10/8/02; 10/23/02.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 6-10, 13 and 14 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 6-10 and 13 is/are rejected.
- 7) ☒ Claim(s) 14 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                             | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____  |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)         | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other:  |

### DETAILED ACTION

1. Claims 6-10 and 13-14 are pending.
2. In view of amendments filed 10/8/02 and 10/23/02, the following rejections remain.
3. The following is a quotation of the first paragraph of 35 U.S.C. 112:  
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
4. Claims 6-10 and 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a monomer protein comprising an amino acid sequence of SEQ ID NO: 2 wherein the amino acid sequence belonging to TGF $\beta$  superfamily of which cysteine at position 83 related to a dimer formation of the protein has been replaced with alanine for induce differentiation of osteoblast and increases alkaline phosphatase activity *in vitro*, does not reasonably provide enablement for (1) *any* MP52 protein wherein the cysteine related to dimer formation has been replaced by an amino acid selected from the group consisting of serine, threonine, alanine and valine, (2) *any* "agent" comprising the monomer protein of "MP52 protein" wherein the cysteine related to dimer formation has been replaced by an amino acid selected from the group consisting of serine, threonine, alanine and valine containing an effective amount of *any* "monomer protein" for "preventing" and treating any disease affecting bone and/or cartilage such as osteoporosis, osteoarthritis, arthroseitis, bone fracture, a lack of root of teeth and a tooth socket. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient

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to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only one monomer protein comprising an amino acid sequence of SEQ ID NO: 2 that belongs to the TGF $\beta$  superfamily, having an amino acid substitution of cysteine for alanine at position 83 of SEQ ID NO: 2 wherein the monomer protein induces differentiation of osteoblast and increases alkaline phosphatase activity in vitro (See page 5, lines 10-15, pages 12-13).

The specification does not teach how to make and use any "MP52 protein", any "agent" comprising any "monomer protein" because said "MP52 protein", "agent" and "monomer protein" without SEQ ID NO: have no structure such as the amino acid sequence or chemical structure, much less function, in turn, for "preventing" or treating any disease affecting bone and or cartilage. Given the indefinite number of undisclosed "MP52 protein", "agent", and "monomer protein", there is insufficient guidance as to which cysteine or cysteines within said undisclosed "MP52 protein", "agent", and "monomer protein" should be replace for amino acid such as serine, threonine, alanine and valine and whether after substitution, the resulting undisclosed "MP52 protein", "agent", and "monomer protein" will retain the function as the MP52 comprising the amino acid sequence of SEQ ID NO: 2.

Ngo *et al.*, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (see Ngo *et al.*, 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Mason *et al.*, of record, teach amino acid substitution of *any* cysteine residues (there were 9 of them in total) of a monomer protein such as activin A comprising an amino acid sequence that belongs to the TGF- $\beta$  superfamily from cysteine to alanine fails to maintain either the structure and/or functions such as intracellular assembly and secretion of the dimer protein (see page 327, column 1, in particular) or loss biological activity (See activin cysteine mutant 4 and 12, page 327, column 2, in particular) or loss of receptor binding activity (See Receptor Binding Activities of activin cysteine mutant 4 and 12, page 327, column 2, in particular). Mason *et al* further teach that the equivalent in TGF $\beta$ 1 in which the cysteine residue corresponding to residue 77 when changed to a serine residue, the resulting secreted monomer has no bioactivity (See page 330, column 1, first paragraph, in particular). Further, there are no in vivo working examples in the specification as filed demonstrating that any undisclosed "MP52 protein", "agent" and

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"monomer protein" are functional, let alone being effective for "preventing" and treating any disease mentioned above. An agent or protein for "preventing" and "treating" any disease in the absence of *in vivo* data is unpredictable for the following reasons: (1) the agent or protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the agent or protein; (2) the agent or protein may not reach the target area because, i.e. the agent or protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the agent or protein unsuitable for *in vivo* therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of *Ex parte Aggarwal*, 23 USPQ2d 1334 (PTO Bd. Pat. App. & Inter. 1992). The specification does not describe nor enable any agent, any MP52 protein or any monomer protein other than those defined by SEQ ID NO: 2. Even if the MP52 protein or agent is limited to the amino acid sequence of SEQ ID NO: 2, there are no *in vivo* working example that substituting the cysteine related to dimer formation for an amino acid such as serine, threonine, alanine, and valine can "prevent" any disease affecting bone and/or cartilage. The term "prevent" as defined in Webster's II New Riverside University Dictionary as "to avert or to anticipate or to counter in advance". The specification does not teach how to predict who will be effective for the treatment. The specification does not teach how to extrapolate data obtained from *in vitro* assays such as differentiation of osteoblast cell lines by measuring alkaline phosphatase activity to the development of effective *in vivo* prevention of any disease related congenital bone and or cartilage, commensurate in scope with the claimed invention. The specification does not teach MP52 protein comprising an amino acid sequence as shown in SEQ ID NO: 2 wherein the cysteine related to dimer formation has been replaced by an amino acid such as serine, threonine and valine and whether after substitution has any biological activity, much less preventing or treating any disease affecting bone and/or cartilage.

Other than the specific monomeric MP52 protein comprising the amino acid sequence of SEQ ID NO: 2 wherein the cysteine related to dimer formation has been replaced with alanine mentioned above for inducing differentiation of osteoblast *in vitro*, the specification does not teach how to make and use *any* monomer protein and *any* agent mentioned above for preventing and treating *any* disease affecting bone and/or cartilage. Since the MP52 protein are not enabled, it follows that agent comprising the monomer protein and the MP52 protein containing any

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amount of monomer protein for preventing and treating any disease affecting bone and/or cartilage such as the ones mentioned is not enabled.

For these reasons, the specification as filed fails to enable one skill in the art to practice the invention without undue amount of experimentation. As such, further research would be required to practice the claimed invention.

Applicants' arguments filed 10/8/02 and 10/23/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) MP52 is a well-known protein and the active form of which is normally present as a mature dimeric protein, (2) new claims 13 and 14 do not protect monomeric protein of the TGF- $\beta$  superfamily and each amino acid substitution is directed to MP52 proteins. The position of the relevant cysteine is indicated at lines 32 to 35 of page 3 of the specification. (3) Other forms like the naturally occurring mature MP52 with additional alanine (120 amino acids) or with alanine and arginine (121 amino acids) at the N-terminus are comparably active as can be seen by WO95/04819 and WO 97/04095. The term MP52 protein is intended to encompass such forms of MP52 which have been long known in the state of the art under the proviso that the cysteine for dimer formation is substituted by any one of alanine, valine, serine or threonine. The critical position unexpectedly can tolerate exchanges and still retain activity is obvious when taking into the general teaching of Dayoff et al.

In response to applicant's argument that MP52 is a well known protein, the term "MP52" as the sole means of identifying the claimed protein renders the claims indefinite because these are merely laboratory designations which do not clearly define the claimed product, since different laboratories may use the same laboratory designations to define completely distinct protein. Further, a database search just Medline alone for the term "MP52 protein" has resulted in 10437 hits and all of them are drawn to irrelevant proteins. Clearly, "MP52" as the sole means of identifying the claimed protein is insufficient to identify the claimed protein. In short, MP52 protein without SEQ ID NO has no specific structure.

In response to item 2, newly added claim 13 recites any MP52 protein (monomer protein 52) wherein the cysteine related to dimer formation has been replaced by amino acid such as serine, threonine, alanine or valine because it MP52 protein without SEQ ID NO has no specific structure. Further, the specification on page 3 at lines 32 to 35 discloses only the relevant cysteine within the amino acid sequence of SEQ ID NO: 2 encoding by the polynucleotide of SEQ ID NO: 1 to be substitute for alanine only. The specification does not discloses (1) any

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MP52 protein wherein the cysteine related to dimer formation has been replaced by (2) any amino acid residues such as serine, threonine, and valine, much less retain activity. Note, the instant claims now recite limitations, which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as-filed. This is new matter.

In response to item 3, the other forms of naturally occurring mature MP52 such as the ones disclose in WO95/04819 and WO 97/04095 publication are from the background of the invention and not even incorporated by references. Thus, said MP52 disclosed in WO95/04819 and WO 97/04095 publication are not part of Applicant's invention.

5. Claims 6-10 and 13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* MP52 protein wherein the cysteine related to dimer formation has been replaced by an amino acid selected from the group consisting of serine, threonine, alanine and valine, (2) *any* "agent" comprising the monomer protein of "MP52 protein" wherein the cysteine related to dimer formation has been replaced by an amino acid selected from the group consisting of serine, threonine, alanine and valine containing an effective amount of *any* "monomer protein" for "preventing" and treating any disease affecting bone and/or cartilage such as osteoporosis, osteoarthritis, arthroseitis, bone fracture, a lack of root of teeth and a tooth socket.

The specification discloses only one monomer protein comprising an amino acid sequence of SEQ ID NO: 2 that belongs to the TGF $\beta$  superfamily, having an amino acid substitution of cysteine for alanine at position 83 of SEQ ID NO: 2 wherein the monomer protein induces differentiation of osteoblast and increases alkaline phosphatase activity *in vitro* (See page 5, lines 10-15, pages 12-13).

Other than the specific monomer protein comprising SEQ ID NO: 2 having a cysteine residue at position 83 replaced with alanine mentioned above for induces differentiation of osteoblast and increases alkaline phosphatase activity *in vitro*, there is inadequately written description about the **structure associated with function** of *any* "MP52 protein", "agent" and "monomer protein" because said "MP52 protein", "agent" and "monomer protein" without SEQ ID NO: have no structure, much less function. Further, the specification discloses only one MP52

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protein of SEQ ID NO: 2 having only alanine substitution. The specification does not disclose any MP52 protein wherein the cysteine related to dimer formation has been substituted for serine, threonine or valine for "preventing" any disease affecting bone and/or cartilage such as osteoporosis, osteoarthritis, arthrositis, bone fracture, lack of root of teeth and tooth socket. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co.* 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 10/8/02 and 10/23/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) MP52 is a well-known protein and the active form of which is normally present as a mature dimeric protein, (2) new claims 13 and 14 do not protect monomeric protein of the TGF- $\beta$  superfamily and each amino acid substitution is directed to MP52 proteins. The position of the relevant cysteine is indicated from lines 32 to 35 of page 3 of the specification. (3) Other forms like the naturally occurring mature MP52 with additional alanine (120 amino acids) or with alanine and arginine (121 amino acids) at the N-terminus are comparably active as can be seen by WO95/04819 and WO 97/04095. The term MP52 protein is intended to encompass such forms of MP52 which have been long known in the state of the art under the proviso that the cysteine for dimer formation is substituted by any one of alanine, valine, serine or threonine. The critical position unexpectedly can tolerate exchanges and still retain activity is obvious when taking into the general teaching of Dayoff et al.

In response to applicant's argument that MP52 is a well known protein, the term "MP52" as the sole means of identifying the claimed protein renders the claims indefinite because these are merely laboratory designations which do not clearly define the claimed product, since different laboratories may use the same laboratory designations to define completely distinct protein. A database search just Medline alone for the term "MP52 protein" has resulted in 10437 hits and all of them are drawn to irrelevant proteins. Clearly, "MP52" as the sole means of identifying the claimed protein is insufficient to identify the claimed protein.

In response to item 2, newly added claim 13 recites any MP52 protein (monomer protein 52) wherein the cysteine related to dimer formation has been replaced by amino acid such as



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serine, threonine, alanine or valine because it MP52 protein without SEQ ID NO has no specific structure. Further, the specification on page 3 at lines 32 to 35 discloses only the relevant cysteine within the amino acid sequence of SEQ ID NO: 2 encoding by the polynucleotide of SEQ ID NO: 1 to be substitute for alanine. The specification does not discloses (1) any MP52 protein wherein the cysteine related to dimer formation has been replaced by (2) any amino acid residues such as serine, threonine, and valine, much less retain activity. Note, the instant claims now recite limitations which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as-filed. This is new matter.

In response to item 3, the other forms of naturally occurring mature MP52 such as the ones disclose in WO95/04819 and WO 97/04095 publication are from the background of the invention and not even incorporated by references. Thus, said MP52 disclosed in WO95/04819 and WO 97/04095 publication are not part of Applicant's invention.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 6-10 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Mason *et al* (Molecular Endocrinology 8(3): 325-332, 1994; PTO 1449).

Mason *et al* teach an agent comprising a monomer protein such as activin A comprising an amino acid sequence that belongs to the TGF- $\beta$  superfamily of which cysteine at position 80 related to a dimer formation of the protein has been replaced with another amino acid such as alanine or serine (see page 327, column 1, in particular). Claims 6-10 are included in this rejection because the agent comprising the same monomer protein; an agent is an agent irrespective of its intended use. Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 10/8/02 and 10/23/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) claims 13 and 14 do not protect monomeric protein of the TGF-beta superfamily and only to MP52 proteins, (2) Mason *et al* describes monomeric protein activin A and only refers to monomeric TGF- $\beta$ 1. Members of the TGF beta superfamily include

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BMPs and GDFs and MP52 belongs to the GDFs. (3) Mason et al describes that TGF- $\beta$ 1 and activin A do not show any or only little activity in the monomeric form.

In response to applicant's arguments (items 1 and 3) that the reference fails to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., do not protect monomeric protein of the TGF-beta superfamily and only to MP52 proteins and activity) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In response to applicant's argument that Mason et al describes monomeric protein such as activin A and members of the TGF beta superfamily includes BMPs and GDFs and MP52 belongs to the GDFs, the claims as written do not recite a specific protein identified by a SEQ ID NO. Mason *et al* teach an agent comprising a monomer protein such as activin A, which is a member of the TGF supperfamily as the claimed MP52 protein. Further, a product is a product irrespective of how it is used.

8. Claim 14 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.
9. The following new ground of rejection is necessitated by the amendment filed 10/8/02 and 10/23/02.
10. The following is a quotation of the first paragraph of 35 U.S.C. 112:  
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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11. Claims 6-10 and 13 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The "serine, threonine and valine" in Claim 13 represents a departure from the specification and the claims as originally filed because said "serine, threonine and valine" do not appear in the specification as originally filed according to the passage indicated by applicant's amendments.

12. No claim is allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

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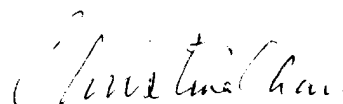
15. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.

Patent Examiner

Technology Center 1600

February 10, 2003

  
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